Epithelial-Mesenchymal Interactions in Wounds

Treatment of Palmoplantar Wounds by Nonpalmoplantar Pure Epidermal Sheet Grafts

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Background: Palms and soles differ from other body sites in terms of clinical and histologic appearance and response to mechanical stress. We previously reported that palmoplantar fibroblasts regulate keratin 9, which is a marker of palms and soles.

Objective: To treat palmoplantar wounds by using non-palmoplantar pure epidermal sheets as a graft.

Design: Nonrandomized controlled trials.

Setting: University dermatology and plastic surgery services.

Patients: Forty-eight patients with palmoplantar wounds caused by burns, trauma, chronic ulcers, and the resection of malignant tumors, such as squamous cell carcinoma and acral lentiginous melanoma.

Interventions: The patients received nonpalmoplantar pure epidermal sheet grafts (n=14), nonpalmoplantar donor site skin grafts (n=17), or palmoplantar donor site skin grafts (n=17).

Main Outcome Measures: Clinical and histologic findings.

Results: The pure epidermal sheets were successfully grafted and gradually demonstrated the adoption of a palmoplantar phenotype when reticular dermis of the recipient site remained. The epidermis showed hyperkeratosis and acanthosis by histologic studies and stained positively for keratin 9 in all of the suprabasal keratinocyte layers like palmoplantar-type skin. Pure epidermal sheets were placed on deeper wounds after the wounds had an artificial dermis applied and adopted the palmoplantar phenotype without erosions and ulcerations. Neither nonpalmoplantar split-thickness nor full-thickness skin grafts resulted in a palmoplantar phenotype.

Conclusions: Pure epidermal sheet grafting would be useful for the treatment of palmoplantar wounds as nonpalmoplantar epidermis is much easier to obtain clinically. In addition, secondary procedures are not required to repair the donor site, since this wound is superficial.

Arch Dermatol. 2001;137:621-628

Although skin grafting is one of the oldest surgical procedures, no special technique has been developed for decades except for cultured epithelial sheet grafting\(^1\)\(^2\) and pure epidermal sheet grafting.\(^3\)\(^4\) Free skin grafts seem to be underused when compared with free flaps in the field of plastic and reconstructive surgery and are regarded as old-fashioned surgical methods. The mechanism of graft healing involves angiogenesis, which occurs in 3 phases: the plasmatic imbibition phase, the inosculatory phase, and the revascularization phase; however, it is difficult to explain the mechanism of pure epidermal component graft healing. Recently, we proposed a fourth phase, keratinocyte activation phase, in the healing process of pure epidermal sheet grafts and split-thickness skin grafts but not full-thickness skin grafts.\(^6\) The fact that split-thickness skin grafts take better than full-thickness skin grafts can be explained through this keratinocyte activation phase. We compared the new method of pure epidermal sheet grafts with the traditional skin grafts (split-thickness and full-thickness skin grafts) and suggest that pure epidermal sheet grafts have several advantages for the treatment of specialized areas.

Palms and soles differ from other body sites in terms of clinical and histologic appearance,\(^7\)\(^8\) response to mechanical stress,\(^9\) and the distribution of keratin 9 (K9).\(^10\) Therefore, it is difficult to treat palmoplantar skin defects caused by acute injury, burns, chronic ulcers (such as diabetic gangrene and ischemic ulcer), and the resection of malignant tumors (such as squamous cell carcinoma and acral lentiginous melanoma). Treatment of Dupuytren con-
PATIENTS AND METHODS

SURGICAL PROCEDURES AND NONRANDOMIZED CONTROLLED TRIALS

All operations were performed after patients gave informed consent in accord with the ethical standards of the Helsinki Declaration of 1975. From January 31, 1994, to July 5, 1999, 48 Asian patients with palmpoplantar skin defects, caused by acute burns, injury, and the resection of squamous cell carcinoma and acral lentigious melanoma, were treated with autologous skin grafts at Osaka University Medical Hospital, Osaka, Japan. For 17 palmpoplantar wounds (patient age range, 3-74 years), palmpoplantar skin was used as donor tissue for the grafts. Full-thickness and split-thickness skin grafts were performed for 8 and 9 patients, respectively. For another 17 palmpoplantar wounds (patient age range, 3-75 years), non-palmpoplantar skin (with dermal component) was used as the donor tissue. Full-thickness and split-thickness skin grafts were performed for 14 and 3 patients, respectively. For the remaining 14 palmpoplantar wounds (Table 1), pure epidermal sheet grafts derived from nonpalmpoplantar sites were used.

Briefly, split-thickness skin was harvested from non-palmpoplantar sites of the body, such as groin, thigh, and abdomen, by either a razor or a dermatome after aseptic treatment. The donor wound was covered with occlusive dressing therapy (Tegaderm Plus; 3M Health Care, St Paul, Minn), as it was shallow and healed within 1 week. The donor skin was put into a 50-mL disposable centrifuge tube (Corning Inc, Corning, NY) and then incubated with dispase, 500 U/mL (Godo Shusei, Tokyo, Japan) in Dulbecco modified Eagle medium at 37°C for 30 minutes. After the epidermal side of the skin was placed on gauze (Adaptic, Johnson & Johnson, Arlington, Tex; or Sofraulle; Hoechst Marion Roussel, Tokyo, Japan), as a supporter to prevent shrinkage, dermal components were meticulously removed with forceps. The pure epidermal sheets were washed 3 times with isotonic sodium chloride solution and grafted on the various depths of palmpoplantar skin defects.

To report nonrandomized controlled trials among 3 groups, initial wound size was first calculated. If erosions and/or ulcersations occurred within 1 year after grafting, erosions and/or ulcersations were considered present. If pigmentation was observed in the grafted skin 1 year after grafting, pigmentation was considered present. Biopsy specimens were taken from each patient group during 1 year after the grafting was performed. If K9-positive cells were observed in all of the suprabasal keratinocyte layers of grafted skin, K9 expression was considered present. In 14 of 17 palmpoplantar skin grafts, 15 of 17 nonpalmpoplantar skin grafts, and 10 of 14 nonpalmpoplantar pure epidermal sheet grafts, erosions and/or ulcersations and pigmentation were followed up for 2 years. Finally, 1 palmpoplantar wound site was grafted with both pure epidermal sheet and split-thickness skin derived from a nonpalmpoplantar site.

HISTOLOGIC STUDIES

The samples obtained by biopsy were sectioned in 2 pieces. The first section was processed for routine hematoxylin-cosin staining. The other piece was processed for immunofluorescence assay by sectioning at −20°C (5 µm), fixing with cold acetone, and then incubating with anti-human K9 antibodies (Mab to Cytokeratin 9 Multi-epitope Cocktail; PROGEN, Heidelberg, Germany) at 4°C overnight. After washing with phosphate-buffered saline containing 0.1% Tween 20, the samples were incubated with fluorescein–5-isothiocyanate–conjugated goat affinity-purified anti–guinea pig IgG antibody (Cappel, Westchester, Pa) at room temperature for 60 minutes. The samples that were incubated with preimmune serum were used as negative controls.

STATISTICAL ANALYSIS

Values of wound size were recorded as mean±SE and estimated by t test. Each group of categorical data, such as ulceration, pigmentation, and K9 expression, was compared by the χ2 test.

INDUCTION OF A PALMOPPLANTAR PHENOTYPE BY REMOVING DONOR DERMIS

In a single patient, we used a pure epidermal sheet graft and traditional split-thickness skin graft from a nonpal-
moplantar donor site to cover different parts of the same wound (Figure 1). We compared the differences in skin appearance between the split-thickness skin graft and pure epidermal sheet graft (Figure 1A), which were both derived from nonpalmoplantar skin (anterior thigh) and were grafted onto the deep dermal defect of the sole. Reticular dermis of the plantar recipient site partly remained among the fat domes because the dermis-fat interface is also undulated like the epidermal-dermal interface (Figure 1B).

Both grafts took well and healed without contraction (Figures 1C-D). Whereas the traditional nonpalmoplantar skin graft (that included the donor dermal component) continued to show a nonpalmoplantar phenotype with hyperpigmentation and hyperkeratosis as previously described,12 the pure epidermal sheet graft demonstrated the adoption of a palmoplantar phenotype with hypopigmentation 2 years after grafting (Figure 1E).

The sample for histologic study in this patient was obtained from the area that included the split-thickness skin graft, pure epidermal sheet graft, and normal sole (Figure 1F). The epidermis of the split-thickness skin graft (Figure 2A, left) showed acanthosis and elongation of saw-toothed rete ridge by histologic studies (Figure 2B), whereas that of pure epidermal sheet graft (Figure 2A, middle) showed thick stratum corneum and acanthosis (Figure 2C) similar to plantar epidermis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age at Surgery, y</th>
<th>Recipient Site</th>
<th>Donor Site</th>
<th>Follow-up Period, mo</th>
<th>Keratin 9 Expression</th>
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<tr>
<td>1</td>
<td>61</td>
<td>Sole (DW)</td>
<td>Anterior thigh</td>
<td>48</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>Sole (SW)</td>
<td>Groin</td>
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<td>+</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>Sole (SW)</td>
<td>Groin</td>
<td>33</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
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<td>Sole (SW+DW+FW)</td>
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<td>+</td>
</tr>
<tr>
<td>5</td>
<td>44</td>
<td>Sole (DW)</td>
<td>Abdomen</td>
<td>31</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>45</td>
<td>Palm (DW)</td>
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<td>+</td>
</tr>
<tr>
<td>7</td>
<td>19</td>
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<tr>
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<tr>
<td>9</td>
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<td>Buttock</td>
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<td>NP</td>
</tr>
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<td>46</td>
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<td>16</td>
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<td>68</td>
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<td>NP</td>
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<tr>
<td>14</td>
<td>48</td>
<td>Palm (FW+A)</td>
<td>Anterior thigh</td>
<td>12</td>
<td>+</td>
</tr>
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</table>

* DW, deep wound on which subcutaneous tissue layers remain; SW indicates superficial wound on which dermis remains; FW, full wound that contains no dermal components including fatty layers; +, keratin 9–positive cells in all the suprabasal keratinocyte layers; A, artificial dermis; and NP, not performed.

Figure 1. Macroscopic observations of a pure epidermal sheet graft and traditional split-thickness skin graft. A, Schematic illustration. STSG indicates split-thickness skin graft; PESG, pure epidermal sheet graft. To cover the same deep dermal defect of the sole (B), we used a PESG and traditional STSG from the same nonpalmoplantar donor site (C). Both grafts took well and without contraction 1 week after grafting (D). Whereas the STSG continued to show a nonpalmoplantar phenotype with hyperpigmentation and hyperkeratosis, the PESG demonstrated the adoption of a palmoplantar phenotype with hypopigmentation 2 years after grafting (E). The sample for histologic study (shown in Figure 2) was obtained from the area including the STSG, PESG, and normal sole (F). Dots and arrowheads in D through F indicate the border of PESG.
There were no K9-positive cells in the epidermis of traditional skin grafts (Figure 2E, left, and F), whereas the K9 distribution in the entire suprabasal keratinocyte layers in pure epidermal sheet graft (Figure 2E, middle, and G) was similar to that of plantar epidermis (Figure 2E, right, and H). These results suggest that pure epidermal sheet grafts derived from nonpalmoplantar donor areas would be useful for the treatment of the deep dermal defects of palms and soles.

Figure 2. Microscopic observations of a pure epidermal sheet graft (PESG) and traditional split-thickness skin graft (STSG). Both were derived from a nonpalmoplantar donor site and were grafted onto the same deep dermal defect of the sole. The sample for histologic study was obtained from the area including the STSG, PESG, and normal sole (see Figure 1). The epidermis of the STSG (A, left) showed acanthosis and elongation of sawtoothed rete ridge (B) by hematoxylin-eosin stain, whereas that of PESG (A, middle) showed thick stratum corneum and acanthosis (C) similar to normal plantar epidermis (A, right, and D). There were no keratin 9 (K9)-positive cells in the epidermis of STSG (E, left, and F), as measured by immunohistochemical examinations with anti–human K9 antibodies. On the other hand, the K9 distribution in the entire suprabasal keratinocyte layers in PESG (E, middle, and G) was similar to that of plantar epidermis (E, right, and H).

NECESSITY OF THE RETICULAR DERMIS

We next examined whether the palmoplantar dermis, fat, and fascia can all induce the palmoplantar phenotype in nonpalmoplantar epidermis (Figure 3). At first, plantar skin defects were classified into 3 types: shallow wound where dermal layers remained, deep wound where subcutaneous tissue layers remained, and full wound to the fascia where no subcutaneous tissue layers remained (Figure 3A-B). A pure epidermal sheet derived from a non-
palmoplantar site, ie, anterior thigh, was grafted on all of these plantar wounds. The grafted pure epidermis took well at 1 week after grafting in all layered wounds (Figure 3C). The pure epidermis grafted on the shallow wound (SW) gradually demonstrated the adoption of a palmoplantar phenotype at 2 months after grafting (Figure 3D). The epidermis placed on the deep wound (DW) and full wound (FW) became both scaly and hypertrophic at 6 months after grafting (Figure 3E). The epidermis on the DW finally demonstrated the adoption of a palmoplantar phenotype, whereas hypertrophic scar was still observed under the epidermis on the FW 2 years after grafting (Figure 3F).

Whereas adequate expression of K9 was observed in the grafted epidermis on both shallow (dermal layer) and deep (subcutaneous tissue layer) wounds, footprints were observed unlike traditional nonpalmoplantar skin grafts on palms and soles at 2 years after grafting. The epidermis on the full wound (fascia layer) also became scaly at 2 months after grafting (Figure 3D) and became slightly dark at 6 months (Figure 3E). It finally demonstrated the adoption of a palmoplantar phenotype at 2 years after grafting (Figure 3F). In addition to the hypopigmentation, footprints were observed unlike traditional nonpalmoplantar skin grafts on palms and soles at 2 years after grafting. The epidermis on the full wound (fascia layer) also became scaly at 2 months after grafting and gradually demonstrated the adoption of a palmoplantar phenotype at 2 years, but hypertrophic scar was still observed under the epidermis (Figure 3F).

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and deep (subcutaneous tissue layer) wounds at 1 year after grafting, the full (fascia layer) wound showed only rare K9-positive cells (data not shown). Finally, the full wound showed the K9 distribution in the entire suprabasal keratinocyte layers at 2 years after grafting. These results suggest that palmoplantar subcutaneous tissue layers may be required to induce a complete palmoplantar phenotype within 1 year.

**THE USE OF ARTIFICIAL DERMIS**

Delayed skin grafting may result in higher graft take and better cosmetic appearance, probably because of the formation of healthy granulation tissue with hyperproliferative fibroblasts. Deep palmoplantar wounds were covered with artificial dermis (Terudermis; Terumo, Tokyo, Japan) for 2 weeks to obtain healthy granulation tissue. This wound was then grafted with pure epidermal sheets. The results in 2 of our patients are shown in Figure 4 and Figure 5. Both wounds gradually showed a typical plantar appearance with a slight hypertrophic scar development in the center of the graft. The grafted hypertrophic skin became dark at 4 months after grafting (Figure 5F). The expression of K9 in the grafted epidermis at 6 months after grafting was seen in all the suprabasal keratinocyte layers as being similar to that of normal palmoplantar epidermis (data not shown). The use of artificial dermis seemed to accelerate the induction time of the palmoplantar phenotype.

**NONRANDOMIZED CONTROLLED TRIALS**

Nonrandomized controlled trials were performed in our clinic from January 31, 1994, to July 5, 1999 (Table 2). Patients with palmoplantar wounds received nonpalmoplantar pure epidermal sheet grafts (n=14; Table 1), nonpalmoplantar donor site skin grafts (n=17), or palmoplantar donor site skin grafts (n=17). Nonpalmoplantar grafts resulted in erosions and/or ulcerations in 7 (41%) of 17 cases because of their fragility and sensitivity to mechanical stress. They were also cosmetically unacceptable because of their pigmentation in all of 17 cases. In addition, the expression of K9, the marker of palmoplantar epidermis, was not observed in these nonpalmoplantar grafts despite the hyperkeratotic change that was seen on histologic examination.

On the other hand, skin grafts derived from palmoplantar donor sites and nonpalmoplantar pure epidermal sheets were both durable and cosmetically acceptable. The expression of K9 was continuously observed after the transplantation in both grafts. One problem with the palmoplantar grafts was the limited amount of tissue available. However, the pure epidermal grafts derived from nonpalmoplantar areas were obtained easily and were comparable to palmoplantar skin.

**COMMENT**

**MESENCHYMAL-EPITHELIAL INTERACTIONS**

In this study, we have evaluated the use of pure epidermal sheet grafts derived from nonpalmoplantar donor skin on palmoplantar wounds. The removal of the dermal component from the graft was necessary to focus on the heterotypic epithelial-mesenchymal interactions. Nonpalmoplantar pure epidermal sheets on both shallow (dermal depth) and deep (subcutaneous tissue depth) wounds resulted in a complete palmoplantar phenotype of the grafts. When these grafts were applied to deeper wounds (fascia depth), the grafts developed hypertrophic scars, and...
no marginal hyperkeratosis or hyperpigmentation was seen. Traditional nonpalmoplantar donor skin grafts heal with hyperkeratosis and pigmentation.\textsuperscript{12}

Because K9 is exclusively expressed in suprabasal keratinocyte layers of soles and palms and is also seen around acrosyringia, ie, sweat gland ducts in nonpalmoplantar epidermis,\textsuperscript{7,8,10} it plays a role in supporting mechanical stress and may be associated with the epidermal thickness. In vitro study shows that mechanical stress can induce a special keratin, which probably correlates with K9, in nonpalmoplantar keratinocytes.\textsuperscript{9} In addition, K9 expression in keratinocytes represents an intrinsic program, once acquired.\textsuperscript{13,17} According to our present data, adequate induction of K9 expression did occur by 2 years after grafting in the nonpalmoplantar pure epidermal sheets that were grafted on all layered palmo-plantar wounds. However, K9 expression was not observed in traditional graft sites that were obtained from nonpalmoplantar donor sites despite mechanical stress. Nonpalmoplantar fibroblasts might inhibit K9 induction by mechanical stress in vivo.

Dermal factor enhances keratinocyte growth and differentiation.\textsuperscript{18-21} We previously reported that palmoplantar fibroblasts, especially derived from the papillary dermis, can induce K9 in nonpalmoplantar keratinocytes in vitro.\textsuperscript{15} Our present data also imply that mesenchymal-epithelial interactions play an important role in the complete induction of the palmoplantar phenotype in nonpalmoplantar epidermis. Interestingly, when artificial dermis was applied to deep palmoplantar wounds followed by pure epidermal sheet grafts, these grafts showed the palmoplantar phenotype within 6 months after grafting. Dermal fibroblasts around the palmoplantar wounds may have migrated between the grafted epidermis and the wound, thereby inducing K9 expression in the keratinocytes. Besides these epidermal-dermal interactions, palmoplantar keratinocytes located around the sweat glands in the wounds may help the epidermal sheets to obtain the palmoplantar phenotype. Palmoplantar keratinocytes around the sweat glands may extend into the grafted epidermis because the pure epidermis does not contain nonpalmoplantar dermal components, which may disturb this extension in traditional skin grafts. To further test the hypothesis that mesenchymal-epithelial interactions induce palmoplantar phenotype in nonpalmoplantar epidermis, we are experimenting on palmoplantar wounds that were grafted from nonpalmoplantar donor sites. These grafts are being injected with cultured palmoplantar fibroblasts after suction blisters are made in the grafts.

**PURE EPIDERMAL SHEET GRAFTING**

Treatment of palmoplantar wounds has been difficult because palmoplantar skin differs from nonpalmoplantar skin in terms of supporting mechanical stress. As compared with traditional skin grafts, pure epidermal sheet grafts derived from nonpalmoplantar sites have several

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**Figure 5.** Prior application of an artificial dermis to the fascia layer defect of the sole followed by nonpalmoplantar pure epidermal sheet grafting. The fascia layer defect of the sole was covered with an artificial dermis for 2 weeks (A) and was then grafted with a nonpalmoplantar pure epidermal sheet. The graft took well at 1 week after grafting (B). The graft showed slight hypertrophic scar formation at 2 weeks (C) and 4 weeks (D) after grafting. The graft became hyperpigmented 4 months after grafting (E), but at 6 months (F) became hypopigmented like normal palmoplantar epidermis.
advantages. Nonpalmoplantar pure epidermal sheets are easy to obtain and harvest clinically. Because nonpalmoplantar pure epidermal sheets change their phenotype after being placed on palmoplantar wounds, these grafts are functionally durable, do not ulcerate, and are cosmetically acceptable without becoming dark and showing marginal hyperkeratosis.

Furthermore, pure epidermal grafting requires less technique. Pure epidermis is easily obtained by enzymatic treatment of superthin split-thickness skin. These thin epidermal sheets are easier to fix to the recipient site than traditional skin grafts because only compression is necessary, and no suture is needed. Secondary procedures are not required to cover the donor site. The decreased volume of the pure epidermal sheets compared with the traditional skin grafts allows rehabilitation with weight bearing to be started earlier, since dermal vessel compression does not occur in epidermal sheets. Severe contracture does not occur in the pure epidermal sheet grafts. In addition, pure epidermal sheets are not fragile, and their graft take can be confirmed easily.

A disadvantage of these grafts is that the adoption of a palmoplantar phenotype takes a long time (more than 6 months) when these grafts are placed on deep wounds that contain no subcutaneous tissue layers. Previous application of an artificial dermis to deep wounds resulted in accelerated induction of the palmoplantar phenotype of the epidermal sheets (within 6 months).

In summary, pure epidermal sheet grafting is useful for the treatment of shallow palmoplantar wounds, where the subcutaneous tissue layers remain. Supplementation of dermal components with artificial dermis may be required for treatment with pure epidermal sheet grafting on deep palmoplantar wounds, where the subcutaneous tissue layers do not remain.

Table 2. Comparison of Pure Epidermal Sheet Graft With Orthodox Skin Grafts at 1 Year*

<table>
<thead>
<tr>
<th>Group</th>
<th>NPP PESG</th>
<th>NPP Skin Graft</th>
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<tr>
<td>Wound size, cm²†</td>
<td>12.27 ± 4.14</td>
<td>26.77 ± 6.72</td>
<td>4.24 ± 0.68</td>
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<tr>
<td>Erosions and/or ulcerations, No. (%)‡</td>
<td>0/14</td>
<td>7/17 (41%)§</td>
<td>0/17</td>
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<tr>
<td>Pigmentation, No. (%)¶</td>
<td>0/14</td>
<td>17/17 (100%)</td>
<td>0/17</td>
</tr>
<tr>
<td>Positive K9 expression, No. (%)¶¶</td>
<td>11/11 (100%)</td>
<td>0/3</td>
<td>4/4 (100%)</td>
</tr>
</tbody>
</table>

* NPP PESG indicates coverage of palmoplantar wounds by nonpalmoplantar pure epidermal sheet grafts; NPP skin graft, coverage of palmoplantar wounds by nonpalmoplantar donor-site skin grafts; PP skin graft, coverage of palmoplantar wounds by palmoplantar donor-site skin grafts.
† Values are mean ± SE. NPP PESG vs NPP skin graft, P = .08; NPP PESG vs PP skin graft, P = .10; NPP skin graft vs PP skin graft, P = .005.
‡ NPP PESG vs NPP skin graft, P = .009; NPP PESG vs PP skin graft, P < .001; NPP skin graft vs PP skin graft, P = .004.
§ Full thickness, 5 of 14; split thickness, 2 of 3. NPP PESG vs NPP skin graft, P < .001; NPP PESG vs PP skin graft, P < .001.
¶ Keratin 9-positive cells in all of the suprabasal keratinocyte layers of grafted skin. Biopsy was not performed in 3 patients in the NPP PESG group, 14 in the NPP skin graft group, and 13 in the PP skin graft group. NPP PESG vs NPP skin graft, P = .003; NPP PESG vs PP skin graft, P < .001; NPP skin graft vs PP skin graft, P = .03.

Accepted for publication December 26, 2000.

This study was supported in part by the Osaka Medical Research Foundation for Incurable Disease, Osaka, Japan.


We thank Todd Helfman, MD, for the review of the manuscript and thoughtful suggestions on our experimental design. We also thank Satomi Okamoto and Yuka Nakatani for their excellent histologic studies.

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